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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/937,066	ALPAR ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,11-17,20-22 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 5, 6, 11-17, 20-22 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The amendment filed June 2, 2008 has been entered. Claim 1 has been amended. Claims 2-4, 7-10, 18-19, 23-36 and 38-43 are cancelled. Claims 1, 5-6, 11-17, 20-22 and 37 are under consideration in this office action.

Withdrawal of Rejections

2. The following rejections have been withdrawn in view of applicants' amendment and arguments:

a) The rejection of claims 1, 3, 6, 11-17, 37 and 40-43 under 35 U.S.C. 103(a) as being unpatentable over Eyles (1998. Vaccine. Vol.16(7):698-707) in view of Kotze et al., (J. of Pharm. Sci. Vol.88(2):253-257);

b) The rejection of claims 1, 3, 6, 11-12, 16, 37 and 40-43 under 35 U.S.C. 103(a) as being unpatentable over Illum (WO 97/20576 published June, 1997) in view of Kotze et al., (J. of Pharm. Sci. Vol.88(2):23-257); and

c) The rejection of claims 1, 3, 5-6, 11-12, 20-22, 37 and 40-43 under 35 U.S.C. 103(a) as being unpatentable over Duncan et al., (WO 94/20070 published September 1994) in view of Kotze et al., (J. of Pharm. Sci. vol.88(2):23-257).

Response to Arguments

3. Applicant's arguments with respect to claims 1, 5-6, 11-17, 20-22 and 37 have been considered but are moot in view of the new grounds of rejection.

New Grounds of Rejection Necessitated by Amendments

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Ruprecht et al., (WO 92/05791).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof.

Ruprecht et al., teach prevention or treatment of a mammal infected with a virus comprising providing an active agent in the of a therapeutic polysaccharide effective amount of the polysaccharide in a pharmaceutically acceptable carrier (page 2, lines 16-21). Ruprecht et al., teach a therapeutic polysaccharide is useful to treat a disease or disorder in an amount to produce a significant physiological effect in a patient (page 3, lines 23-26). Ruprecht et al., teach sulfated chitosan derivative N-carboxymethyl-

chitosan-N, O-sulfate (page 4, lines 18-21). Ruprecht et al., teach combination therapy with other anti-retroviral agents in treatment of patients (page 4, lines 24-26).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1, 5-6, 11-15 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Amsden et al., (WO 99/57176).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof. Claim 5 is drawn to the composition further comprising a cationic polypeptide, cationic polyamino acid, a quaternary ammonium compound or a mixture thereof. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres, microparticles or liposomes. Claim 12 is drawn to the particles being microparticles. Claim 13 is drawn to the first material capable of forming particles is a polymeric material which has a molecular weight of 100kDa or more. Claim 14 is drawn to the first material capable of forming particles comprises poly-(L-lactide). Claim 15 is drawn to the ratio of the first

material capable of forming particles to the polycationic carbohydrate is from 99:1 to 9:1 w/w. Claim 20 is drawn to the composition further comprising a polyamino acid or cationic pluronic.

Amsden et al., teach the application of microspheres composed of biodegradable, biocompatible polymer and contains a bioactive agent dispersed therein (page 23, lines 3-6). Amsden et al., teach delivering a bioactive agent to a subject in need of treatment (page 23, lines 15-16). Examples of suitable bioactive agents include anti-proliferative agents, steroids, analgesics, narcotic antagonists, antibiotics, anti-fungals, anti-histamines, anti-asthmatics, B-blockers and anti-cancer agents (page 23, lines 18-23). Amsden et al., teach therapeutic microspheres comprising a bioactive agent being a pharmacologically active peptide, antigen, or antibody explemplified by a microsphere that bears an infectious agent antigen for vaccination (page 24, lines 1-3). Amsden et al., teach the composition formed into microspheres composed of hydrophilic polymers selected from polysaccharides such as chitosan, N,O-carbomethyl chitosan, O-carboxymethyl chitosan, N-carboxymethyl chitosan, blends, copolymers and combinations of these polymers (page 9, lines 12-26). It is noted that the polycationic carbohydrates capable of forming particles from 99:1 to 9:1 w/w include chitin derivatives, chitosans, cationic polypeptides, polyamino acids; which are all disclosed by Amsden et al. Amsden et al., teach polymers formed into microspheres composed of poly(lactide-co-glycolide) (PGLA) and other lipophilic polymers such as polyesters including but not limited to poly-(L-lactide), poly(lactide) as well as protein or

polypeptide such as poly(amino acids). It is noted that is a polymeric material having a molecular weight of 100 kDa or more.

Therefore Amsden et al., teach the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 3, 6, 11-17, 20-22 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eyles (1998. Vaccine. Vol.16(7):698-707) in view of Amsden et al., (WO 99/57176).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof. Claim 5 is drawn to the composition further comprising a cationic polypeptide, cationic polyamino acid, a quaternary ammonium compound or a mixture thereof. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres, microparticles or liposomes. Claim 12 is drawn to the particles being microparticles. Claim 13 is drawn to the first material capable of forming particles is a polymeric material which has a

molecular weight of 100kDa or more. Claim 14 is drawn to the first material capable of forming particles comprises poly-(L-lactide). Claim 15 is drawn to the ratio of the first material capable of forming particles to the polycationic carbohydrate is from 99:1 to 9:1 w/w. Claim 16 is drawn to the biologically active agent is capable of generating a protective immune response against tetanus, anthrax, diphtheria, or *Yersinia pestis*. Claim 17 is drawn to the biologically active agent comprising a combination of the V antigen of *Y. pestis* or an immunologically active fragment thereof, and the F1 antigen of *Y. pestis* or an immunologically active fragment thereof. Claim 20-22 are drawn to the composition further comprising a polyamino acid or cationic pluronic. Claim 37 is drawn to the biologically active agent being able to produce an immune response against tetanus, anthrax, diphtheria, or *Yersinia pestis* in an animal to which it is administered.

Eyles et al., teach a pharmaceutical composition comprising poly-(L-lactide) microspheres co-encapsulated with *Yersinia pestis* V and F1 subunits that confer protection from pneumonic plague in mice (page 699, col.2). Eyles et al., teach that the F1 antigen confers resistance to phagocytosis and both F1 and V antigens are protective, although there is an additive effect in the combination (page 698, col.2). It is noted that the F1 peptide subunit is a glycoprotein. The commercially purchased poly-(L-lactide) has a molecular weight of 100 kDa and was used in a modified double emulsion solvent evaporation method (page 699, col.2). Eyles et al., teach effective vaccination requires affecting or utilizing musocal surfaces as portals of entry (page 698-699, col.2-1). Furthermore Eyles et al., teach that mucosal vaccination advantageously offers some degree of the induction of systemic immunity in concert

with local responses due to translocation of antigenic material (page 699, col.1). Eyles teach that simple mucosal applications are ineffective because of enzymatic or chemical destruction, combined with poor absorption; therefore encapsulation of antigenic material within microparticulate polymeric carriers such as poly-DL-lactide protect the vaccines from degradation and enhance mucosal and systemic absorption (page 699, col.1). However Eyles et al., do not teach pharmaceutical compositions comprising N-carboxymethyl chitosan.

Amsden et al., has been discussed above as teaching compositions of microspheres containing a bioactive agent dispersed therein (page 23, lines 3-6). Amsden et al., teach therapeutic microspheres comprising a bioactive agent being a pharmacologically active peptide or antigen, or a microsphere composition that bears an infectious agent antigen for vaccination (page 24, lines 1-3). Amsden et al., teach the composition comprising N-carboxymethyl chitosan (page 9, lines 12-26).

Therefore it would have been prima facie obvious at the time of applicants' invention to modify the pharmaceutical composition comprising a biologically active agent as taught by Eyles et al., wherein the modification incorporates the use of N-carboxymethyl chitosan as taught by Amsden et al., in order to provide biodegradable, biocompatible polymers containing a bioactive agent dispersed therein in order to deliver a bioactive agent to a subject in need of treatment. One of ordinary skill in the art would be motivated to modify the microparticle compositions as taught by Eyles et al., because Eyles et al., teach that effective compositions capable of generating a protective immune response require utilizing musocal surfaces as portals of entry; thus

one of ordinary skill in the art would have a reasonable expectation of success in providing microparticle compositions with further significantly increased mucosal absorption which is beneficial to the recipient without the disadvantage of enzymatic or chemical destruction, combined with poor absorption. No more than routine would have been required to modify the composition of Eyles et al., by incorporating N-carboxymethyl chitosan, because Amsden et al., teach it is well known to provide suitable bioactive agents including pharmacologically active antigen within therapeutic microspheres while Eyles teach et al., that the F1 antigen is both a peptide drug and a glycoprotein used within microsphere compositions. Furthermore, the limitations drawn to the ratios of particles to the polycationic carbohydrate are viewed as merely optimizing the experimental parameters and not imparting patentability; thus no more than routine skill would have been required to change the concentration in the well known compositions as taught by Eyles et al., in view of Amsden et al.

Claim Rejections - 35 USC § 103

7. Claims 1, 5-6, 11-17, 20-22 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (WO 97/20576 published June, 1997) in view of in view of Amsden et al., (WO 99/57176).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof. Claim 5

is drawn to the composition further comprising a cationic polypeptide, cationic polyamino acid, a quaternary ammonium compound or a mixture thereof. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres, microparticles or liposomes. Claim 12 is drawn to the particles being microparticles. Claim 13 is drawn to the first material capable of forming particles is a polymeric material which has a molecular weight of 100kDa or more. Claim 14 is drawn to the first material capable of forming particles comprises poly-(L-lactide). Claim 15 is drawn to the ratio of the first material capable of forming particles to the polycationic carbohydrate is from 99:1 to 9:1 w/w. Claim 16 is drawn to the biologically active agent is capable of generating a protective immune response against tetanus, anthrax, diphtheria, or *Yersinia pestis*. Claim 17 is drawn to the biologically active agent comprising a combination of the V antigen of *Y. pestis* or an immunologically active fragment thereof, and the F1 antigen of *Y. pestis* or an immunologically active fragment thereof. Claim 20-22 are drawn to the composition further comprising a polyamino acid or cationic pluronic. Claim 37 is drawn to the biologically active agent being able to produce an immune response against tetanus, anthrax, diphtheria, or *Yersinia pestis* in an animal to which it is administered.

Illum teaches vaccine compositions comprising one or more biologically active agents capable of generating a protective immune response in an animal, an effective adjuvant and the polycationic carbohydrate, chitosan (page 1, lines 1-6). Illum teaches suitable antigens include tetanus toxoid and diphtheria toxoid (pages 4-5, lines 23-1). Illum teaches the pharmaceutical compositions are formulated in the form of microspheres (page 6, lines 22-24). Illum teaches that chitosans are known as mucosal absorption enhancers and upon administration, chitosan enhances the immune response of antigens and provides an enhanced effect upon the host (page 3, lines 1-6). However Illum does not teach pharmaceutical compositions comprising N-carboxymethyl chitosan or a salt thereof.

Amsden et al., has been discussed above as teaching compositions of microspheres containing a bioactive agent dispersed therein (page 23, lines 3-6). Amsden et al., teach therapeutic microspheres comprising a bioactive agent being a pharmacologically active peptide or antigen, or a microsphere composition that bears an infectious agent antigen for vaccination (page 24, lines 1-3). Amsden et al., teach the composition comprising N-carboxymethyl chitosan (page 9, lines 12-26).

Therefore it would have been prima facie obvious at the time of applicants' invention to modify the pharmaceutical composition comprising a biologically active agent as taught by Illum, wherein the modification incorporates the use of N-carboxymethyl chitosan as taught by Amsden et al., in order to provide biodegradable, biocompatible polymers containing a bioactive agent dispersed therein in order to deliver a bioactive agent to a subject in need of treatment. One of ordinary skill in the art

would be motivated to modify the compositions as taught by Illum, because Illum teach the need for chitosans, which are well known mucosal absorption enhancers that also enhance the immune response of antigens; thereby providing a reasonable expectation of success. Thus one of ordinary skill in the art would have a reasonable expectation of success in providing compositions having incorporating N-carboxymethyl chitosan, because Amsden et al., teach it is well known to provide suitable bioactive agents including pharmacologically active antigen within therapeutic microspheres. Finally it would have been advantageous to incorporate the N-carboxymethyl chitosan in the pharmaceutical composition, in order to achieve an enhanced effect upon the host.

Claim Rejections - 35 USC § 103

8. Claims 1, 5-6, 11-15 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan et al., (WO 94/20070 published September 1994) in view of Ruprecht et al., (WO 92/05791).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof. Claim 5 is drawn to the composition further comprising a cationic polypeptide, cationic polyamino acid, a quaternary ammonium compound or a mixture thereof. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres, microparticles or

liposomes. Claim 12 is drawn to the particles being microparticles. Claim 13 is drawn to the first material capable of forming particles is a polymeric material which has a molecular weight of 100kDa or more. Claim 14 is drawn to the first material capable of forming particles comprises poly-(L-lactide). Claim 15 is drawn to the ratio of the first material capable of forming particles to the polycationic carbohydrate is from 99:1 to 9:1 w/w. Claim 20-22 are drawn to the composition further comprising a polyamino acid or cationic pluronic.

Duncan et al., teach compositions comprising: i) biologically active agents, such as immunogens or antigens at pages 4-5 para.1, ii) an adjuvant chemical having adjuvant properties wherein the adjuvants include Pluronic^{TM} block copolymers also known as cationic pluronics and polyamino acids such as polyarnithine at pages 9-10, para. 1; and iii) an acceptable carrier such as a mucoadhesive at page 6, para.1. Duncan et al., further teach that an enhancement in the immune response is observed when the adjuvant is combined with the immunogen and muchoadhesive (pages 10-11, para.2). The antigens are more immunogenic when they are incorporated into the polymeric microparticles, nanoparticles or liposomes (page 2, para.4). However Duncan et al., do not teach pharmaceutical compositions comprising N-carboxymethyl chitosan.

Ruprecht et al., has been discussed above as teaching compositions comprising providing an active agent in the of a therapeutic polysaccharide effective amount of the polysaccharide in a pharmaceutically acceptable carrier and N-carboxymethyl-chitosan (page 2, lines 16-21). Ruprecht et al., teach combination therapy with other anti-retroviral agents in treatment of patients (page 4, lines 24-26).

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known N-carboxymethyl chitosan as taught by Ruprecht et al., and modify the compositions to include the biologically active antigen and agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by Duncan et al., in order to enhance the muchoadhesive properties. One of ordinary skill in the art would have a reasonable expectation of success by modifying the pharmaceutical compositions as taught by Duncan et a., because Duncan et al., teach the need for muchoadhesive which provide further enhancement in the immune response. Thus one of ordinary skill in the art would have a reasonable expectation of success in providing compositions having N-carboxymethyl-chitosan since Ruprecht et al., teach it is well known to provide pharmaceutical compositions comprising N-carboxymethyl-chitosan are effective in patients. No more than routine would have been required to modify the composition of Duncan et al., to instead incorporate the N-carboxymethyl-chitosan into the pharmaceutical composition of Duncan which already comprises a muchoadhesive combined with biological active antigens and cationic pluronic in microparticle formation to achieve enhanced mucosal absorption. Finally it would have been advantageous to incorporate N-carboxymethyl-chitosan in the pharmaceutical composition, in order to achieve an enhanced effect upon the host.

Conclusion

9. No claims allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645